63. A pharmaceutical preparation for administration in vivo to an animal comprising the liposome vesicle-entrapped chemical species according to Claim 62.

C1 cont.

64. A pharmaceutical preparation for parenteral administration in vivo to an animal comprising the liposome vesicle-entrapped chemical species according to Claim 62, wherein the buffer has an osmolarity within the physiological range of an animal, the vesicles are suspended for administration in a bulk solution, and the bulk solution has a pH which is physiologically benign.--

REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.129(a), are respectfully requested.

By the present amendment, claims 27-45 have been deleted in view of the Decision in Interference No. 103,469 ("the '469 Interference"). New claims 46-64 have been added. Support for claims 46 and 52 may be found, at the very least, in prior claims 27-45 and throughout the originally filed specification. Support for the recitation of a "*stable* liposome vesicle-entrapped chemical species" may be found at the very least at page 14, lines 5-19, and in Example 3, page 19, lines 18-25. No new matter is thus being added by this amendment.

Applicant gratefully acknowledges the courtesy extended by Examiner Kishore to his representatives during the Examiner Interview conducted on October 20, 1999.

Turning now to the Official Action, the Examiner has rejected the claims under 35 U.S.C. § 102(c) in view of the Board of Interference's decision and applicant's express abandonment of parent application Serial No. 07/741,305. This rejection is moot in light of the foregoing amendment.

Applicant's new claims are directed to an invention separately patentable from the Count in the '469 Interference. More specifically, the Count was directed to a method of preparing a phospholipid-entrapped cationic, lipophilic drug composition by creating a pH gradient to drive the chemical species or a drug into the liposome. These claims recited the physical chemistry of creating a pH gradient to load the liposome. Mehlhorn's claims, however, were not directed to preparation of a *stable* liposome vesicle-entrapped chemical species.

As asserted by Forssen in its Brief at Final Hearing (Exhibit 1, a copy of which is enclosed herewith):

> The point of dispute relates to Mehlhorn's contention that neither the Nichols nor the Cramer references disclose the preparation of "stable entrapped drug compsoitions." This contention ignores the literal language of the claims and seeks to add a limitation that has no support in the Mehlhorn specification. (Exhibit 1 at page 22)
>
> In characterizing the claimed invention as a method to obtain stable entrapped drug compositions, however, Mehlhorn ignores a fundamental tenet of patent law: the invention must be limited to that which is claimed. *See Environmental Designs Ltd. v. Union Oil Co. of Calif.*, 713 F.2d 693, 699, 218 U.S.P.Q.2d 865, 971 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984). (Exhibit 1 at page 29)

In Forssen's Reply In Support of Its Contingent Motion for Judgment Under 37 C.F.R. § 1.633(a) That Mehlhorn's Claims 51-55 Are Unpatentable (Exhibit 2, a copy of which is enclosed herewith), Forssen stated:

> While Mehlhorn contends "that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification . . ." (Mehlhorn's Opp. at 2), this does not mean that Mehlhorn's method claims may now be construed as claiming "stable entrapped drug compositions." Such a rewriting of the claims is not "reasonable" and finds no support in law or fact. (Exhibit 2 at page 5)

The APJ agreed with Forssen's assertions and granted the Forssen Motion.

Based upon the arguments made by Forssen and the APJ's granting of the Forssen Motions, it is clear that the Mehlhorn claims designated as corresponding to the Count in the '469 Interference were not directed to a method of preparation of a *stable* drug entrapped liposome vesicle.

A method of preparing such stable liposome vesicle-entrapped chemical species is separately patentable from the method of the Count in the '469 Interference. As of the priority date of the instant application, that a stable liposome vesicle-entrapped chemical species could be prepared would have been surprising to a person skilled in the art. As stated by Dr. Cafiso in his Second Declaration submitted in the '469 Interference (Exhibit 3, a copy of which is enclosed herewith):

> Nichols and Deamer thus discloses the physical chemistry involved in using a pH gradient to load catecholamines into a liposome. However, Nichols and Deamer does not teach that the loaded drug composition can be accumulated and thus entrapped in the liposome. Nor was the application of this physical chemistry to drug-entrapped liposomes appreciated by those skilled in the art prior to September 1985. (Exhibit 3 at page 3)

> Cramer and Prestegard, like Nichols and Deamer, discloses the physical chemistry involved in using a pH gradient to load certain simple ionizable molecules into a liposome. However, there is no recognition that the physical chemistry involved in using a pH gradient to load these simple ionizable molecules could also be applied to the accumulation and thus entrapment of a drug composition in the liposome. Nor was the application of this physical chemistry to drug-entrapped liposomes appreciated by those skilled in the art prior to September 1985. (Exhibit 3 at pages 4-5)
>
> As a result of work carried out over the past 10 years, we now recognize that many drugs can be accumulated by a mechanism that utilizes the same physical chemistry described in early articles of Nichols and Deamer, Cramer and Prestegard and Cafiso and Hubbell. However, for those skilled in the art prior to 1985, it would not have been clear whether such a mechanism would work as a general mechanism to accumulate drugs. Drugs such as doxorubicin do contain simple amine functionalities like the catecholamines examined by Nichols and Deamer. However, drugs such as doxorubicin also contain additional structural features not present in catecholamines. Thus, prior to 1985, those skilled in the art, even if they recognized the utility of the physical chemistry described by Nichols and Deamer, would not have known whether the additional structural features present in drugs such as doxorubicin would render the use of this physical chemistry unworkable for drug loading and entrapment. (Exhibit 3 at page 10)
>
> Based upon the above, it is my opinion that, prior to September 17, 1985, those skilled in the art did not recognize the use of a pH gradient for loading a liposome as a method for preparing a stable drug entrapped liposome. (Exhibit 3 at page 10)

As concluded by Dr. Cafiso, there is no teaching or suggestion in Nichols and Deamer or Cramer and Prestegard, nor was there other knowledge in the art prior to September 17, 1985, that a stable entrapped chemical composition could be obtained as now claimed by Mehlhorn. Nor would it have been obvious to one of ordinary skill in the art that a pH gradient could be used to prepare stable entrapped chemical compositions as now claimed by Mehlhorn.

In its Brief at Final Hearing, Forssen misrepresents the teachings of Nichols and Deamers as well as the testimony of Dr. Nichols and Dr. Prestegard in an attempt to support its position. More specifically, similar to the arguments made in its Motion and Reply, Forssen asserted that Nichols and Deamer taught stable entrapped drug compositions, which exhibited stability over roughly 90 minutes (Exhibit 1, Forssen Brief at page 33). However, the testimony of both Dr. Nichols and Dr. Prestegard shows that Nichols and Deamer, as well as Cramer and Prestegard and Fendler, additional references cited by Forssen, fail to show stable drug entrapped liposome compositions as now claimed by Mehlhorn.

Contrary to the assertions of Forssen in its Brief, both Dr. Nichols and Dr. Prestegard agree that Nichols and Deamer does not show a stable liposome, which retains the drug over a period of time. While Nichols and Deamer shows accumulation of drug, i.e., loading, over a period of 90 minutes, it does not show what happens after the liposome is loaded. Thus, it does not show that the liposome is stable and will retain the drug over time. Nichols and Deamer destroyed the pH gradient once the loading was complete.

When asked whether Nichols and Deamer attempted to show how long the material would stay in the liposome, Dr. Prestegard agreed that it did not. The 90 minutes was simply the time period over which maximum loading occurred. *See* Prestegard Testimony (Exhibit 4, a copy of which is enclosed herewith), page 16, line 21 - page 17, line 9. Dr. Prestegard further agreed that Nichols and Deamer was not concerned with maintaining an entrapped drug. *See* Prestegard Testimony, page 17, line 20 - page 18, line 2. With respect to the Cramer and Prestegard paper, Dr. Prestegard stated that "we were not concerned with the

containment of the drug." *See*, page 15, lines 9-10. Dr. Prestegard further agreed that "Fendler doesn't use a gradient to load the liposomes." *See* Exhibit 4 at page 15, lines 19-21.

Thus, Dr. Prestegard's testimony shows that none of the art cited by Forssen in the '469 Interference discloses or even suggests a method of preparing a stable chemical species or drug entrapped liposome, as now claimed by Mehlhorn.

Dr. Nichols further agreed that the 90 minutes disclosed in Nichols and Deamer is the time period over which the liposomes took up the catecholamine in the presence of the pH gradient. *See* Nichols Testimony (Exhibit 5, a copy of which is enclosed herewith), page 35, line 15 - page 36, line 8. Dr. Nichols also agreed that the paper showed that when the pH gradient was destroyed, the catecholamines left the liposomes and were "almost completly effluxed by, after 30 minutes." *See* Exhibit 5 (Nichols Testimony, page 15, lines 7-18, and page 21, lines 2-8). Therefore, there is nothing to show whether the liposome is stable and maintains the drug once loaded.

The claims now of record are thus patentable over the Count, which instead only recites how to load a liposome using a pH gradient. In contrast to the cited art, the instant specification states:

> Drugs encapsulated in this manner are sequestered within the vesicles (e.g., liposomes) until they reach the desired target tissue and are released when the membrane starts to break down and the drug begins to leak at the site of the desired tissue. (A process usually caused by lysosomal activity.) (*See* page 8, lines 10-15 of the instant specification.)

The specification further states:

> After incorporation the chemical will remain in the vesicle for fifteen minutes to several hours depending on the chemicals, until the buffer leaks out of the vesicle. One should be aware that decay of the initial drug content may occur because of dilution of the water volume outside of the vesicles when they are injected into an animal. This decay will generally occur much more slowly than the initial loading process because of favorable effects of the pH gradient on the vectorial movement of the drug across the vesicle membrane. This insures that a drug will reach its targeted tissue before significant leakage out of the vesicles can occur. This time period of usually several hours allows the chemical or drug to be carried to its desired destination and prevents it from acting in areas that would be deleterious to the animal. (*See* page 14, lines 5-19 of the instant specification.)

A method for preparing such stable chemical species or drug entrapped liposomes, having benefits in terms of delivery, was truly surprising at the time of the instant invention.

In view of the above, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 102(c).

Further and favorable action in the form of a Notice of Allowance is respectfully requested. Such action is believed to be in order.

In the event that there are any questions relating to this Amendment, or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone so that prosecution is expedited.

Respectfully submitted,

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